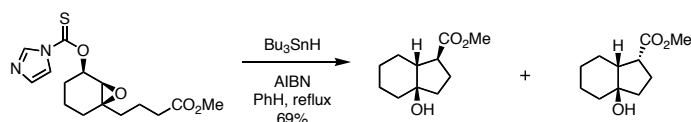


# Radicals In Organic Synthesis

## Features of Radical Reactions

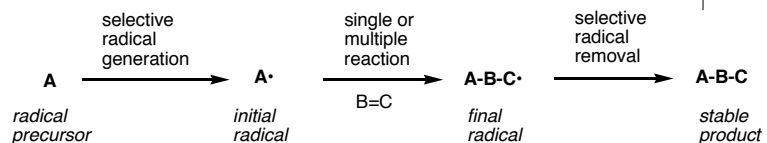
- Reviews: Curran, D. P. In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon Press: Oxford, 1991; Vol. 4; pp 715. Sibi, M. P.; Manyem, S.; Zimmerman, J., "Enantioselective radical processes." *Chem. Rev.* 2003, 103, 3263-3295.

- A major difference between radicals and other reactive species that are employed in synthesis is that virtually all radicals react rapidly with themselves. The lifetime of a transient radical rarely exceeds 1  $\mu$ s and is at the diffusion-controlled limit; the enthalpy of activation of most radical-radical reaction is close to 0 kcal/mol. In general, radical reactions are oxygen-sensitive but water-tolerant. Solvent effects are generally small, but hydrogen-atom abstraction can become a concern in radical reactions of slow or intermediate rates.



- The need to evaluate the relative rates of competing radical reactions pervades synthetic planning of radical additions and cyclizations. Concentrations are therefore very important. The following table contains some representative rate constants:

Reaction	Log A [ $M^{-1}sec^{-1}$ ]	Ea [kcal/mol]	k at 80 °C
Cyclopropyl homoallyl radical fragmentation	13.15	7.05	5.9 E8 $sec^{-1}$
5-exo trig cyclization	10.42	6.85	1.5 E6 $sec^{-1}$
Hydrogen transfer Bu• + HSnBu <sub>3</sub>	9.06	3.65	6.2 E6 $M^{-1}sec^{-1}$
Iodine transfer Bu• + I-CH <sub>2</sub> CO <sub>2</sub> Et	10.4	4.4	4.7 E7 $M^{-1}sec^{-1}$
Thiohydroxamate transfer Bu• + RCO <sub>2</sub> -2-thiopyridyl	9.04	3.95	3.2 E6 $M^{-1}sec^{-1}$
Alkene addition t-Bu• PhCH=CH <sub>2</sub>	7.6	3.42	3.0 E5 $M^{-1}sec^{-1}$



**Chain** reactions comprise initiation, propagation, and termination steps (ex.: Hunsdiecker reaction), and offer often an ideal way to conduct radical additions because of the low concentration of radicals.

Initiation can be accomplished by photochemical or redox reactions, but it is most often accomplished by homolytic bond cleavage of a chemical initiator. Some common initiators are:

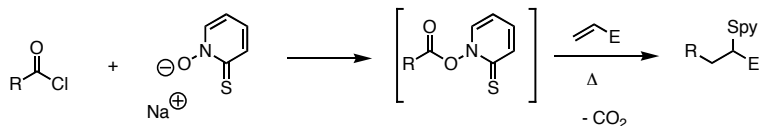
di-t-butyl peroxide	$t_{1/2} = 1 \text{ h at } 150 \text{ }^\circ\text{C}$
t-butyl peroxybenzoate	$t_{1/2} = 1 \text{ h at } 125 \text{ }^\circ\text{C}$
benzoyl peroxide	$t_{1/2} = 1 \text{ h at } 95 \text{ }^\circ\text{C}$
AIBN	$t_{1/2} = 1 \text{ h at } 80 \text{ }^\circ\text{C}$

**CAUTION:** Heating AIBN (azobisisobutyronitrile) produces a deadly chemical, tetramethylsuccinonitrile (TMSN). TMSN is immediately dangerous to life and health (IDLH) at 5 ppm. Cyanide gas has an IDLH at 25 ppm.

As with alkyl radicals, the stereochemical outcome of a reaction of a vinyl radical does not generally depend on the stereochemistry of the precursor. However, there are several examples in which a subsequent reaction of a vinyl radical has been proposed to be more rapid than its inversion.

### Thiohydroxamates (the Barton method)

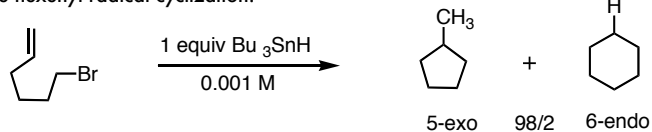
One of the most important chain methods that does not revolve around the chemistry of the trialkyl radical is the Barton thiohydroxamate protocol.



**Mechanism?**

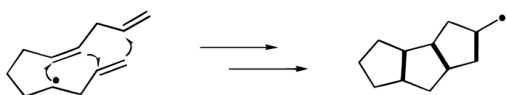
## Radical Cyclizations

The hexenyl radical cyclization:

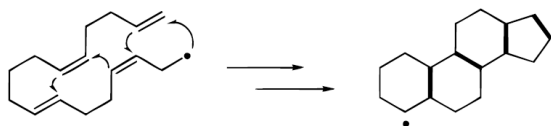


A criss-cross strategy for modhephene (Jasperse, C.P.; Curran, D.P. *J. Am. Chem. Soc.* **1990**, *112*, 5601):

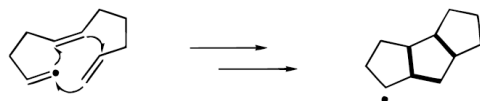
- The "zipper" strategy goes from the middle to the ends.

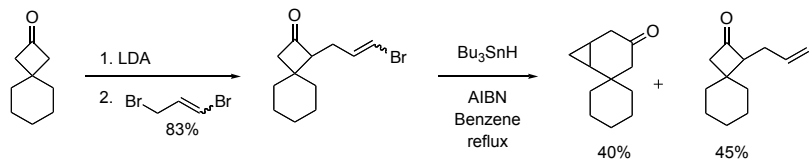


- The "macrocyclization/transannular cyclization" strategy goes from the ends to the middle.



- The "round trip" strategy goes from one end back to the same end.





**Mechanism?**

